Armed Forces College of Medicine

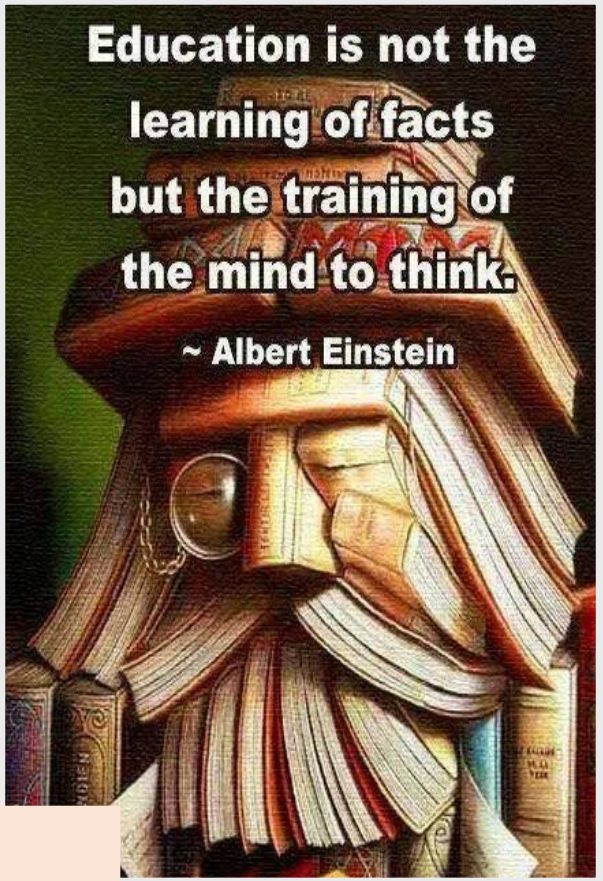
AFCM

Year 2
Endocrine and genitourinary module

Clinical Integrated Cases

Basic Science Principles for Clinical Reasoning

1- Critical thinking
2- Introduction to common forms of disease
3- Apply basic knowledge in a realistic clinical scenario.
4- Interpersonal skills-(share and apply your knowledge)
communication…patient safety



Case co-ordinators

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Presented by

Prof. Drs. Manal Hassan, Lamia Foad

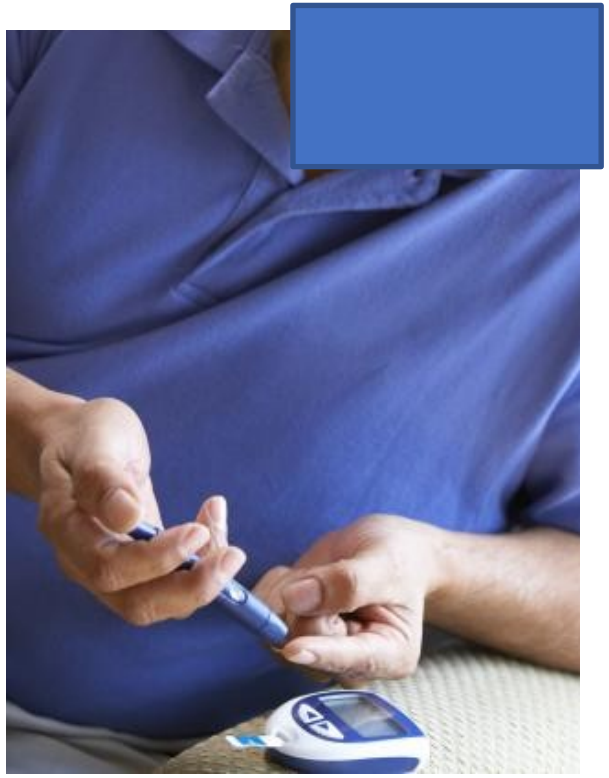
Sharing Departments

- **Internal medicine**
- **Physiology**
- **Biochemistry**
- **Pathology**
- **Histology**
- **Anatomy**
- **Pharmacology**

Case swollen legs

My legs are swollen

Mr. Magdy is a **40** year old man who works as an accountant in a bank. He lives in Sarayelkoba with his wife and 2 children. Magdy has been **diabetic** for 15 years and he is under insulin therapy.



The blood glucose **has not been controlled over the past 10 years**.

My legs are swollen

Magdy noticed **swelling of both lower limbs** for the last 3 months. His wife told him that he must consult an internist.

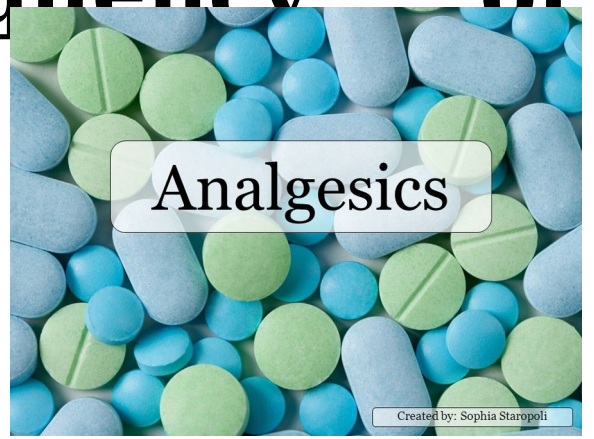
The doctor asked Magdy if he suffers from **dyspnea on exercise** or on sleeping flat.
The doctor also asked about previous history of **jaundice**.
No stool abnormalities

My legs are swollen

The doctor asked about history **puffy eyelids** or **frothy urine**.

The doctor asked also about history of **renal stones, loin pain** or recurrent **urinary tract infection** (**dysuria and frequency of micturition**).

The doctor asked him if he take any **drugs**. Magdy mentioned that he occasionally takes **analgesics (NSAID)** if he feels headache or joint pains.



Past history: Diabetic for 15 years

Family history: irrelevant

My legs are swollen

General Examination

Vital signs examination:

Pulse: 75beats/min

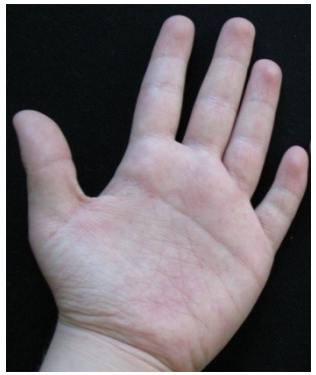
Blood pressure: **150/100 mmHg**

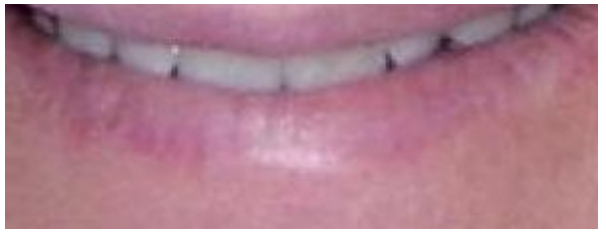
Temperature: 37°C

Respiratory rate: 17/min

The doctor noticed that Magdy appeared **pale** and examined his lips, nails and palms.

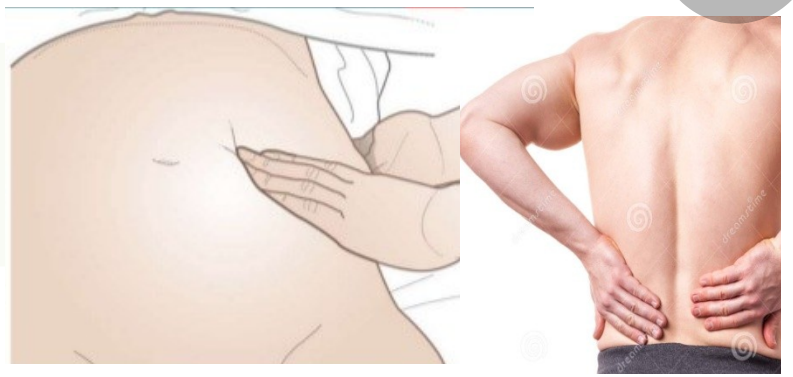
No jaundice nor cyanosis



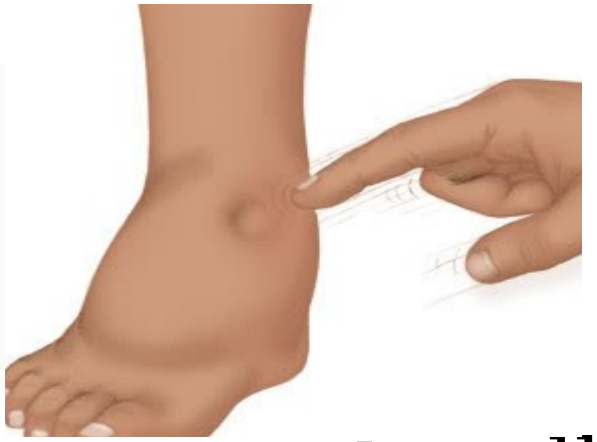


My legs are swollen

Abdominal examination showed **no tenderness in the loin** region.



Lower limb examination showed **bilateral pitting edema** reaching mid leg.

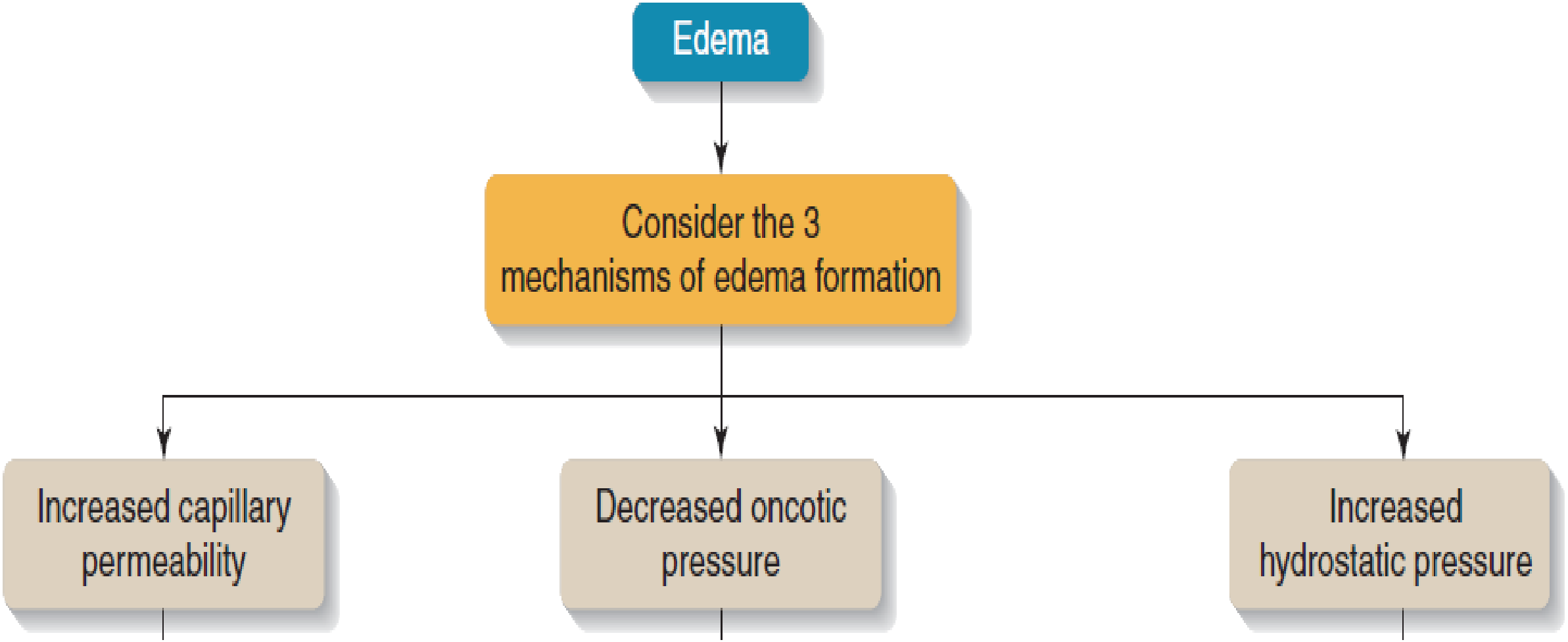


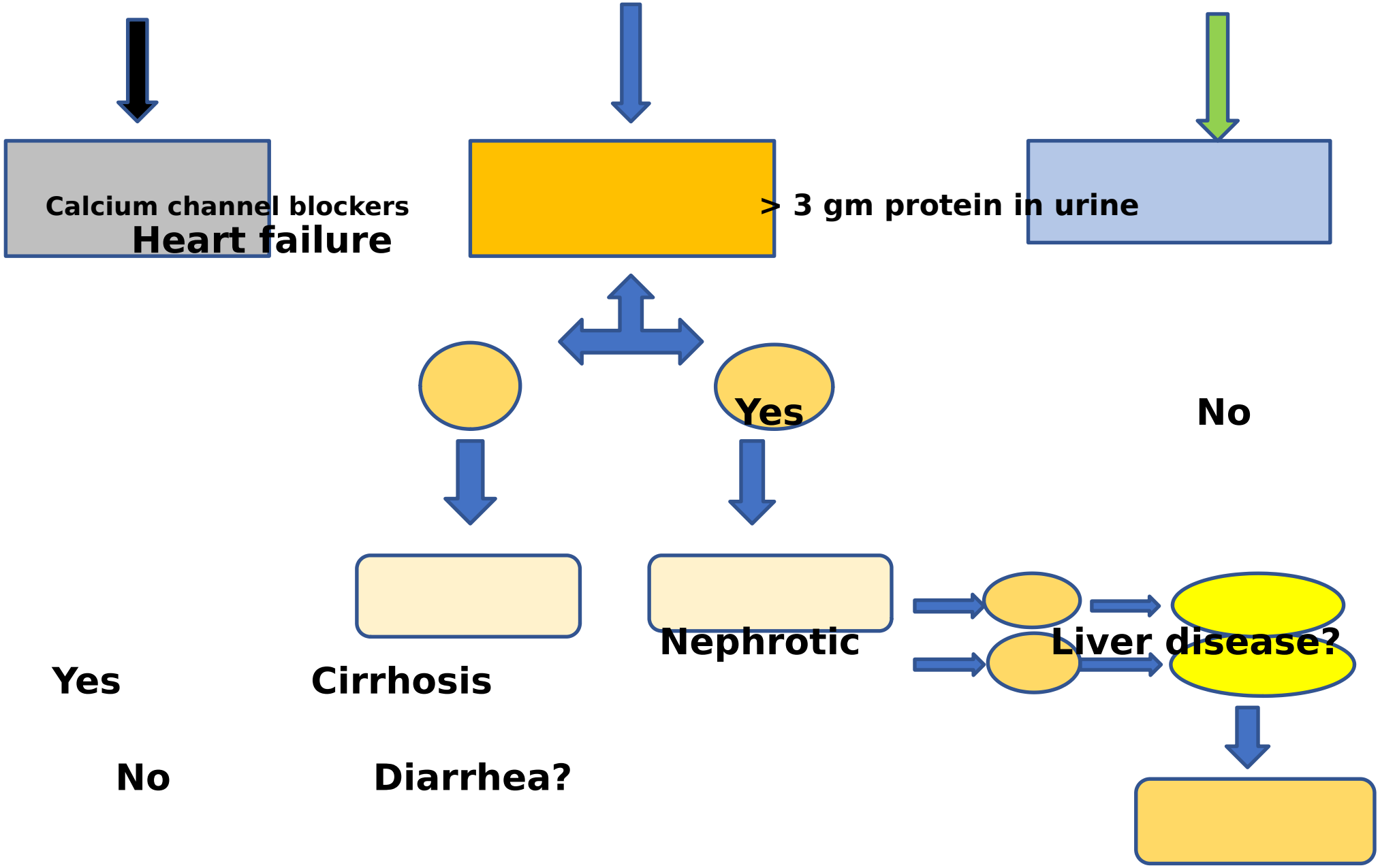
The doctor told Magdy that his diabetes was **not** well controlled and has affected his kidney and so certain investigations must be done. A blood sample was drawn and mid stream urine analysis was done.

The doctor also asked Magdy to lose weight as he is diabetic for 15 years.

1- a. List the patient problems

b. What is the differential diagnosis?


Edema
Consider the 3 mechanisms of edema formation
Increased capillary permeability
Decreased oncotic pressure
Increased hydrostatic pressure


Calcium channel blockers
Heart failure
> 3 gm protein in urine
Yes
No
Yes
Cirrhosis
Diarrhea?
No
Nephrotic
Liver disease?

The doctor asked Magdy if he suffers from **dyspnea on exercise** or on sleeping flat. The doctor also asked about previous history of **jaundice**

2- Why ?

- Dyspnea on exercise or on sleeping flat (orthopnea) to exclude cardiac cause of oedema
- Jaundice : hepatic failure with reduced formation of albumin.

The doctor asked Magdy about History of frothy urine and puffy eyelids
History of renal stones and recurrent UTI.
Family history

Why ?

- Frothy urine with puffy eyelids : nephrotic syndrome.
- Recurrent pyelonephritis, renal stones,
- Family history of diseases like polycystic kidney , as a cause of renal failure which will cause hypervolemia and oedema.

3- What is the importance of drug history in Magdy?

Drugs:

- Ca channel blockers may cause ankle oedema

- or drugs that may cause nephrotic syndrome like gold and penicillamine

- or nephrotoxic drugs that may cause chronic renal failure like Cyclosporine &Tacrolimus.

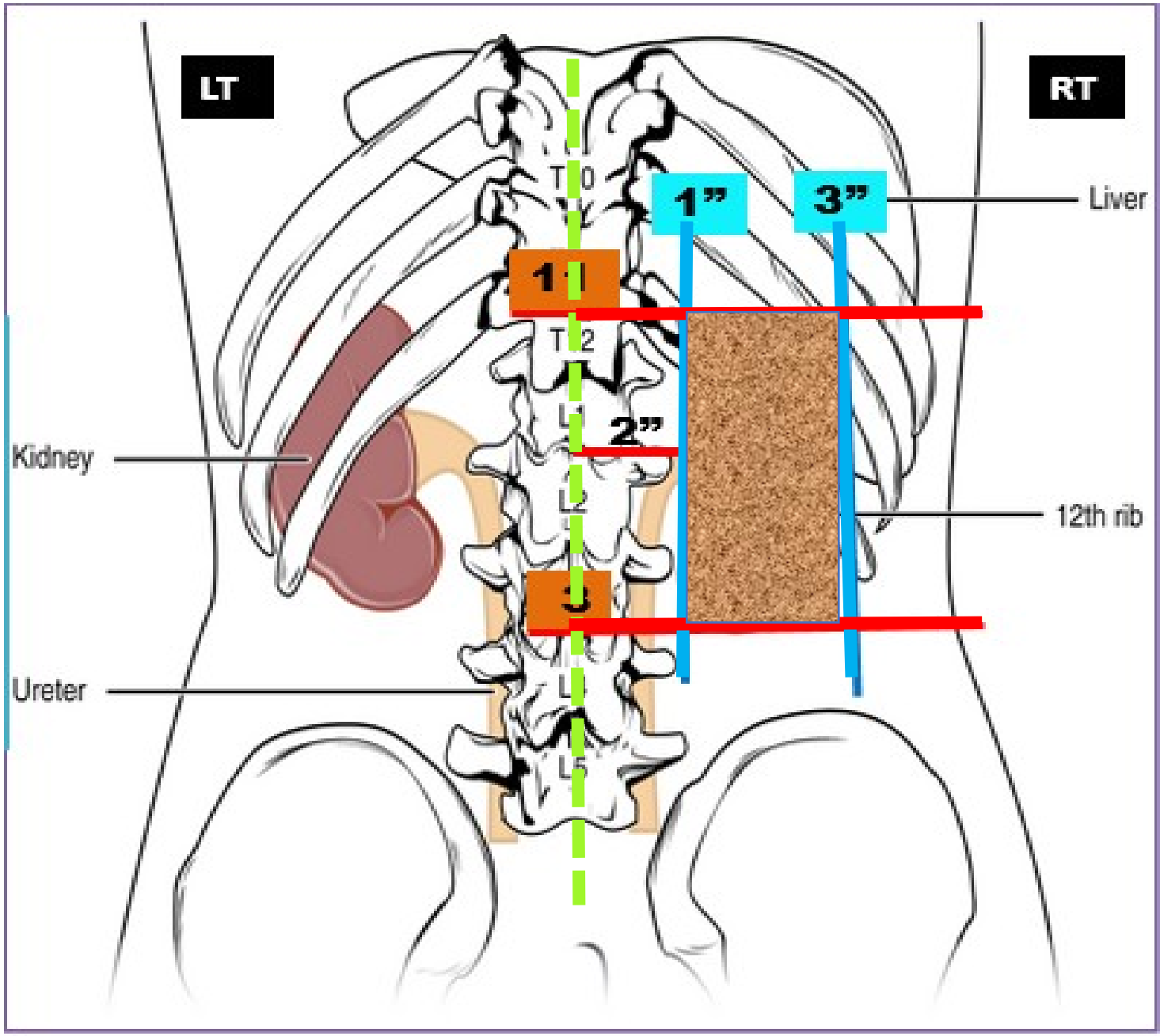
Abdominal examination showed no tenderness in the loin region.

4- Describe the surface anatomy of the kidn

- **Surface anatomy as projected to the posterior surface of the body:**

➢ **The kidney is drawn within “Morris rectangle” (parallelogram)**

- **Two vertical lines: one inch and 3 inches from the midline**



5- What investigations do you suggest to be done?

Patient has long standing Diabetes so the physician has to look for

- Fundus examination
- HBA1C
- Lipid profile
- 24 hours urine collection for proteins .
- Serum albumin
- Renal function (urea, creatinine, and GFR)
- Electrolytes.
- Bicarbonate.
- CBC.

Welcome back

My legs are swollen

The doctor asked for the following blood investigations:

- CBC
- **Fasting and postprandial blood glucose level**
- **HbA1c**
- **Serum creatinine**
- **Urea**
- **GFR**
- Fundus examination
- Lipid profile
- Serum albumin
- Serum bicarbonate

The doctor also asked for ***urine analysis***

My legs are swollen

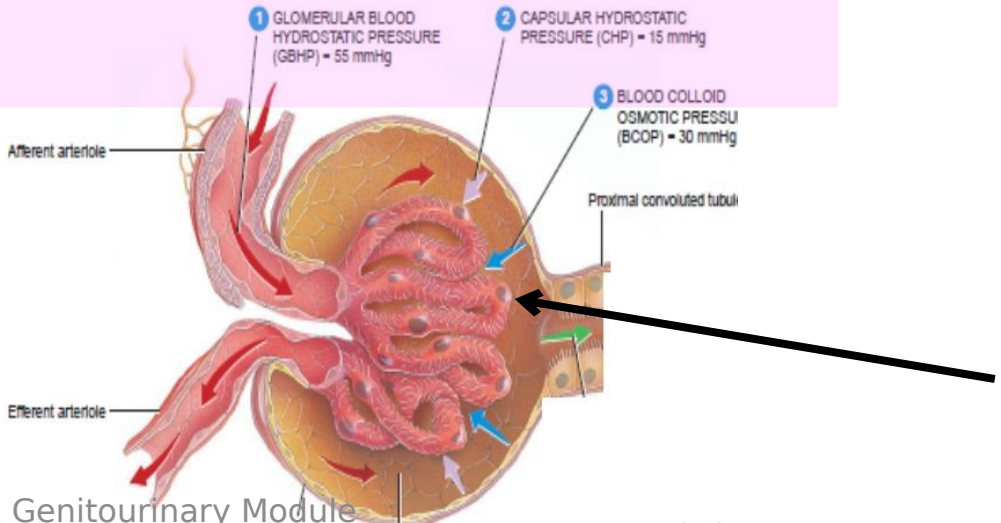
Results of the investigations showed:

HbA1C: **11** (N4.6-5.7%)

Serum creatinine: **2 mg/dl** (N: 0.7 – 1.4mg/dL)

Blood urea: **60mg/dl** (N:20-40mg/dl)

GFR: 40 ml/min.



My legs are swollen

Hb: **9 gm/dL** (N 12-16gm/dL)

Serum Ca: **7.5 mg/dl** (N: 8.5-10.5)

Serum K: **4.5meq/l** (N: 3.5-5)

Urine analysis: showed **2+ proteins**.

24 hours urine collection for protein showed :

Proteinuria of 2000mg/24hr (N < 30mg/24hr)

NB : albuminuria of 30-300mg/24 hrs urine is called microalbuminuria.

More than 300mg/24 hrs urine is called macroalbuminuria.

My legs are swollen

Other investigations showed:

Sodium: 136 meq/ L N: (135-145mEq/L)

Serum Albumin : **3 g/dL** N: (3.4-5.4 g/Dl)

Corrected calcium = serum Ca +0.8 (4-serum albumin)

= 7.5+ 0.8*(4-3)= 7.5+(0.8)

=8.3 mg/dl

Phosphorus : 4mg/dL N: (2.4-4.5mg/dL)

HCO_3: 18mEq/L N: (23- 30 mEq/L)

Lipid profile : high total and LDL cholesterol high triglycerides, Low HDL

According to the investigation results, What is the provisional diagnosis of Magdy?

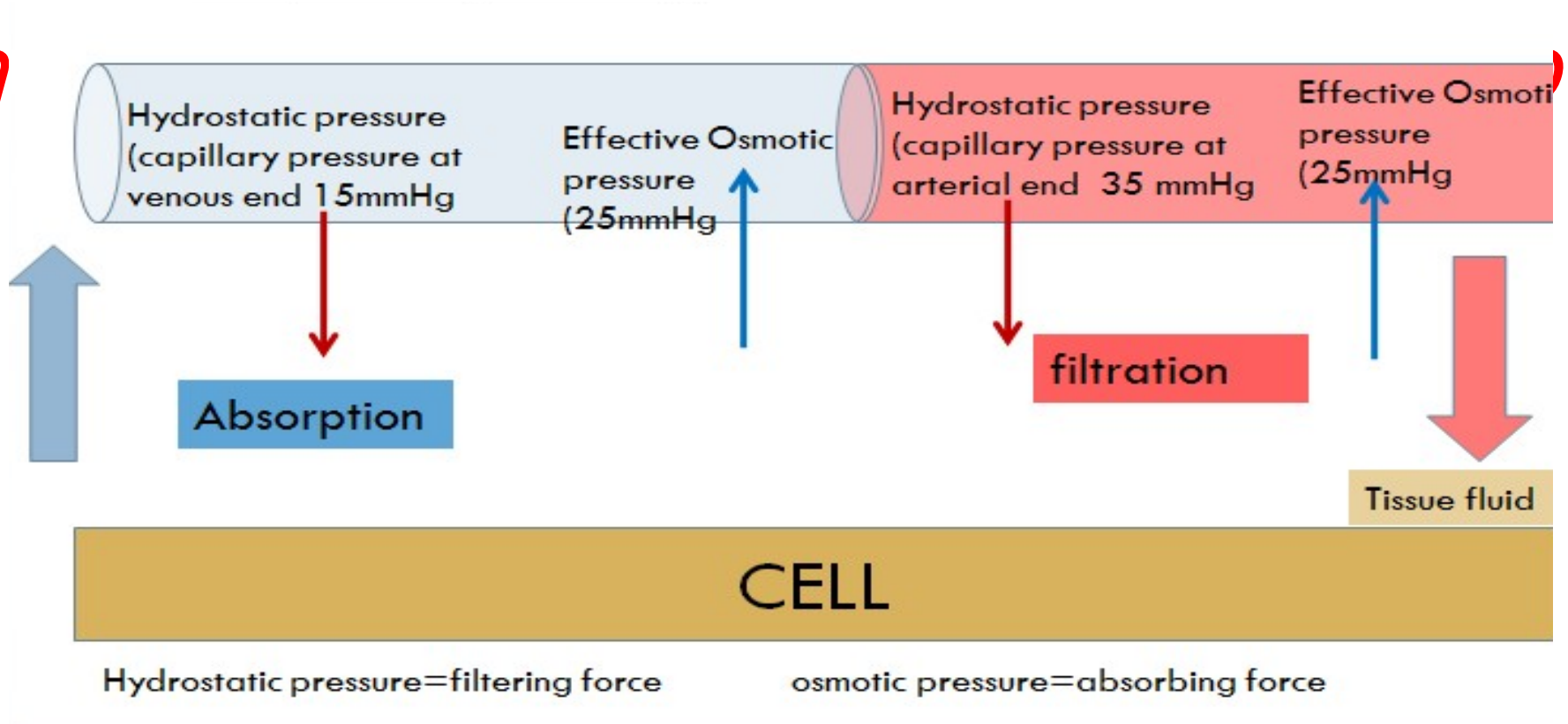
Uncontrolled diabetes mellitus type 1,
uncontrolled hypertension,
diabetic nephropathy,
chronic kidney disease.

6- What is the mechanism of edema in renal disease?

Mechanism of edema in renal disease

- Salt and water retention
- Proteinuria: Decrease plasma oncotic pressure

Increa *tion*



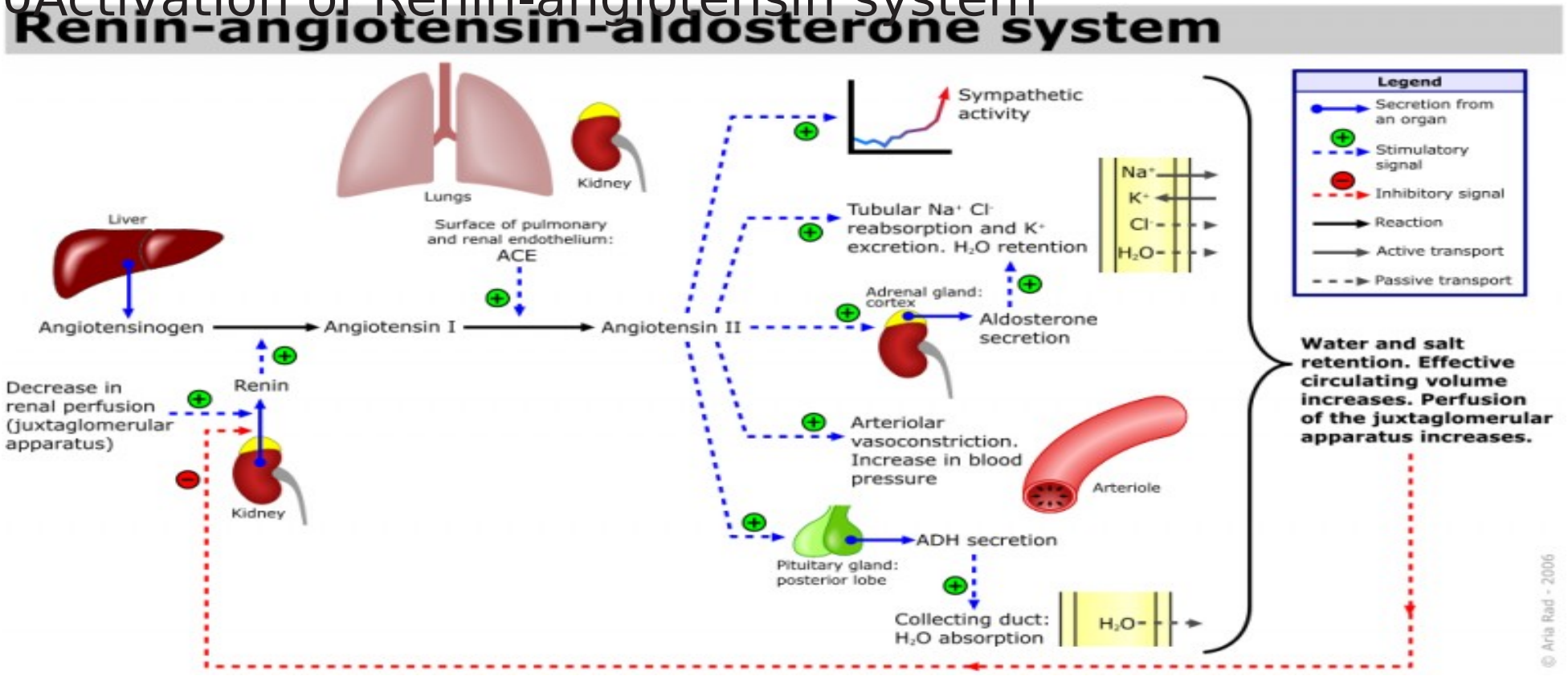
Vital signs:

Pulse:	75/min
Blood pressure:	**150/100**
Temperature:	37°C

Explain the rise in blood pressure

Hypertension is due to:

- Sodium retention and expansion of extracellular fluid volume (ECFV)
- Activation of Renin-angiotensin system



7- What are the cells involved in renin-angiotensin system?

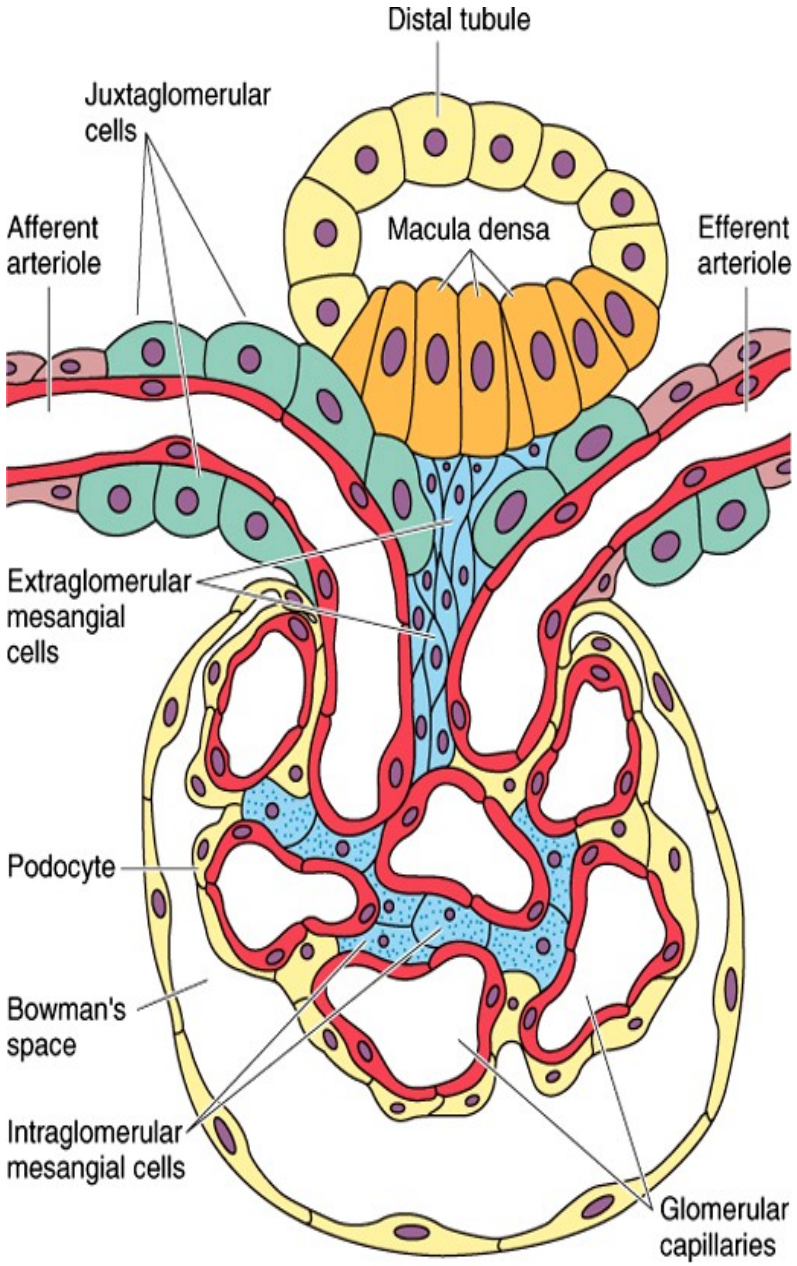
- **Juxtaglomerular apparatus**
  - **Juxtaglomerular cells.**
  - Macula densa cells.
  - Lacis cells "Extraglomerular Mesangium

Juxtaglomerular cells:

Modified smooth muscle cells of the adjacent afferent arteriole (and, sometimes, the efferent arteriole). Their nuclei are spherical, and they have secretory granules in their cytoplasm contain **renin hormone.**

Macula densa cells.

Tall narrow closely packed cells. **They senses the concentration of sodium and chloride ions** in the tubular fluid. A reduction in tubular NaCl stimulates renin release.



Explain the pallor occurring in renal disease?

Patient has anemia: The primary cause is ***insufficient production of erythropoietin*** (EPO) by the diseased kidneys

Other factors:

- Shortened red cell survival in the uremic environment
- Severe hyperparathyroidism with consequent bone marrow fibrosis

HbA1C: 11 (N<6.5)

What is HbA1c?

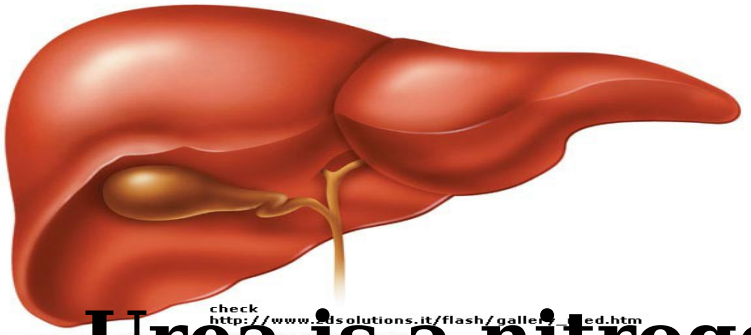
What it significance of its increase?

Serum creatinine: 2mg/dl (N: 0.7 – 1.4mg/dL).
Blood urea: 60mg/dl (N: 20-40mg/dl)

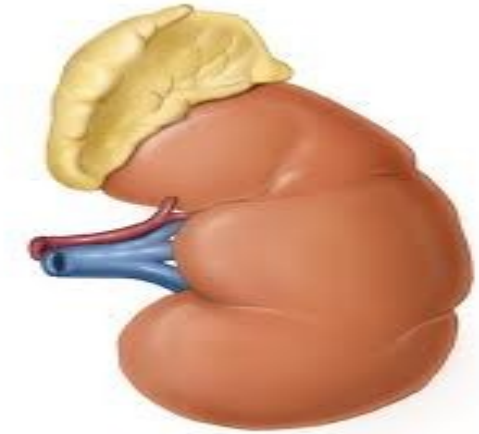
8- What is blood urea and serum creatinine?

Which is more accurate?

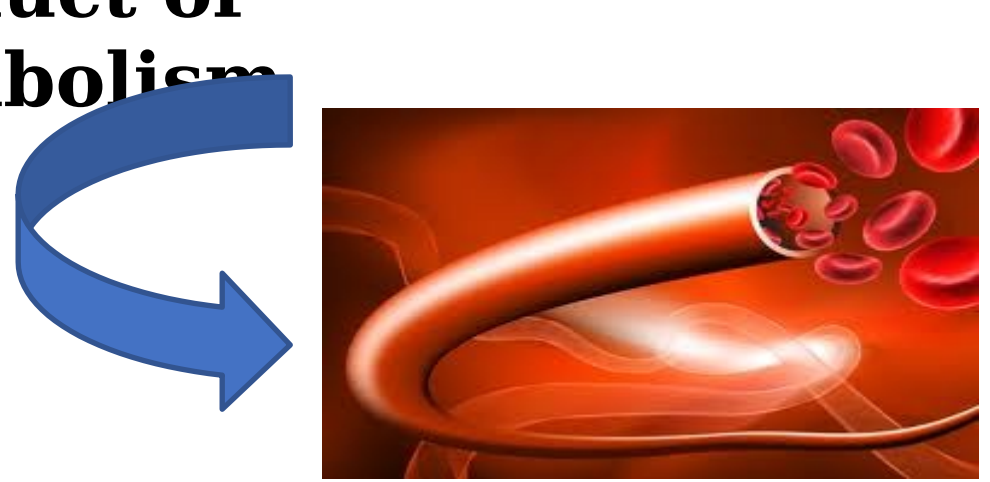
1- UREA



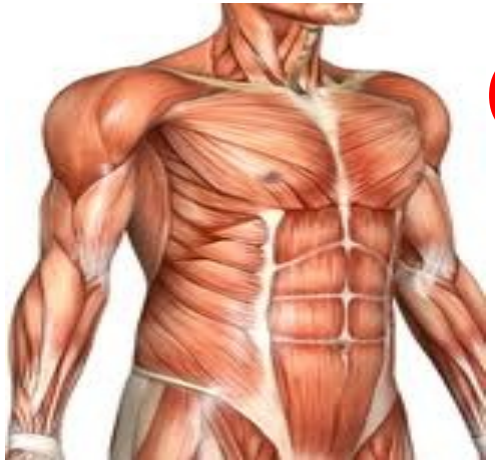
Urea is a nitrogen containing compound formed in the liver as an end product of protein metabolism



Urea filtered in the kidney

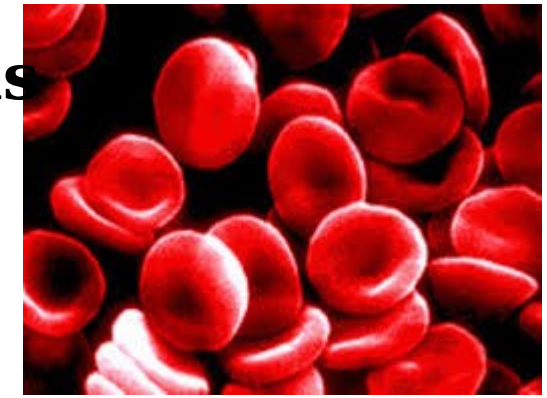


Urea pass in the

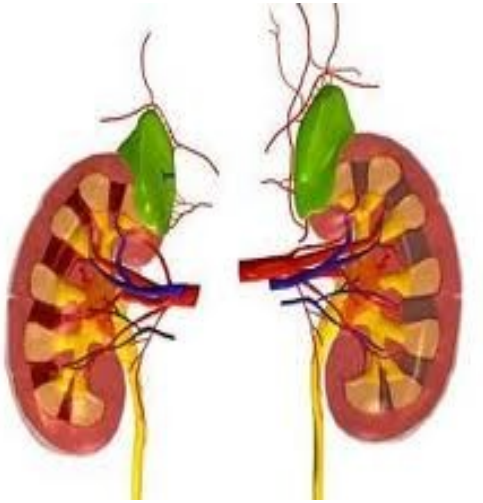


Creatinine

- **Creatinine is a non-protein waste product of creatine phosphate metabolism by skeletal muscle tissue**
- **Creatinine production is continuous and is proportional to muscle mass.**



Creatinine passes in the blood



Creatinine is filtered by the kidney

Normal value of serum creatinine:

Adult males: 0.7 - 1.4 mg/dl: values are slightly higher in males due to larger muscle mass.

Adult females: 0.6 - 1.1 mg/dl.

Children: 0.2 - 1.0 mg/dl

High BUN value may be caused by:

- kidney diseases.
- Blockage of the urinary tract.
- Low blood flow to the kidneys .
- High-protein diet, tissue damage and bleeding in the gastrointestinal tract.

Low BUN value may be caused by:

Very low protein diet, malnutrition, or severe liver damage.

Increased serum creatinine levels are seen in:

- **Glomerulonephritis**
- **Pyelonephritis**
- **Acute tubular necrosis**
- **urinary tract obstruction**
- **Prolonged reduced blood flow to the kidney**
- **Muscle diseases such as acromegaly, and myasthenia gravis.**

Decreased serum creatinine levels are seen in:

- Decreased muscle mass.
- Inadequate dietary protein.
- Muscle atrophy

GFR: 40 ml/min.

9-a What is the normal GFR?

b- How to measure the GFR?

- Normal GFR= ***125ml/min***

- ***GFR is measured by the use of:***
  - Inulin Clearance
  - Creatinine Clearance (clinically)

C=

C= Volume of plasma cleared from substance X per minute

P= Concentration of the substance per 1 ml plasma

U= Concentration of the substance / ml urine.

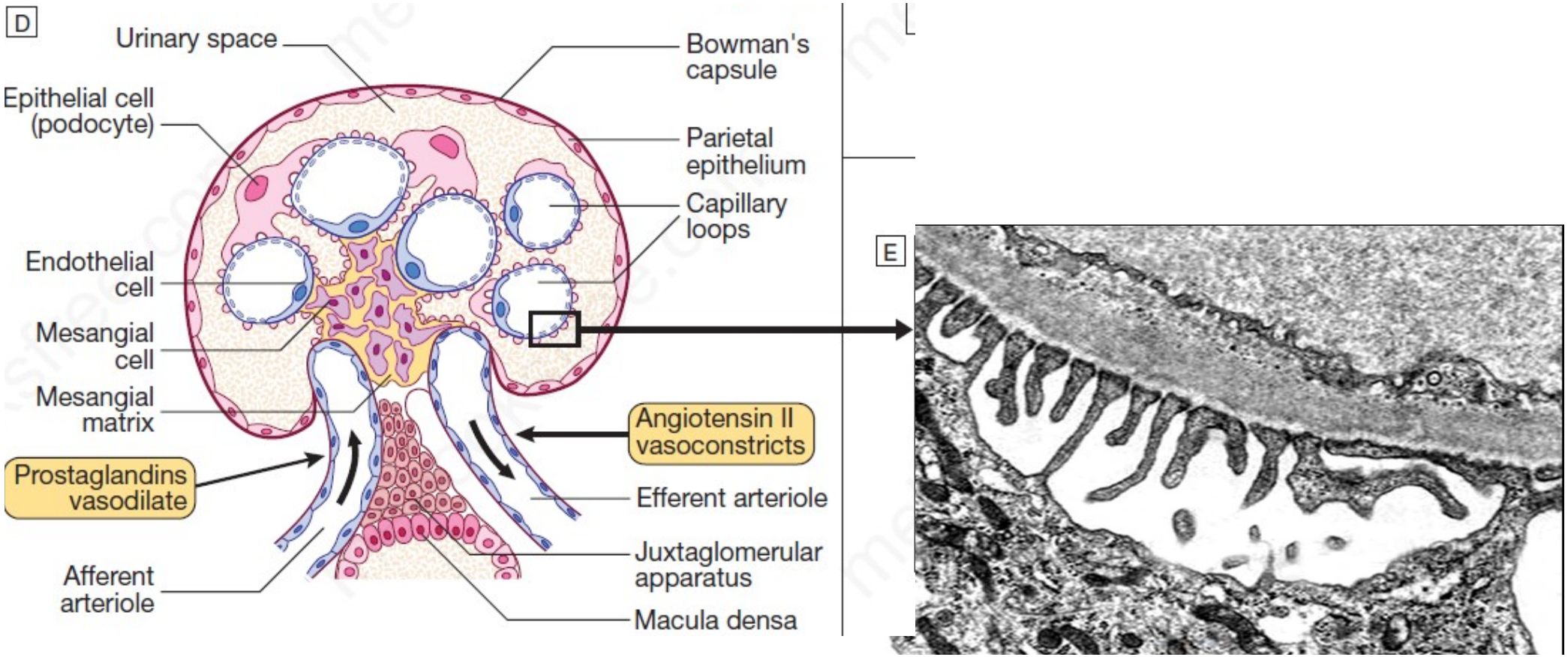
V= Volume of urine / min

- GFR can be estimated from the formula

eGFR=

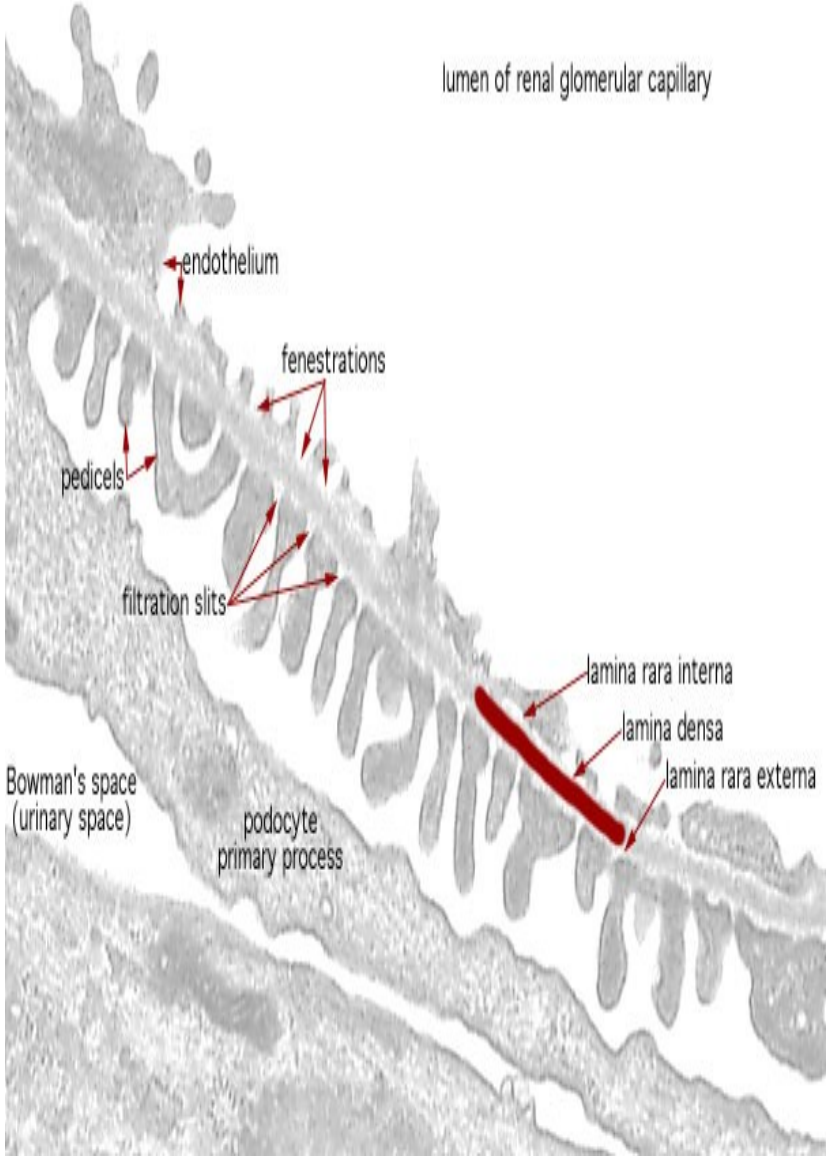
For woman, the estimated GFR is multiplied by 0.85 because muscle mass is less.

What are the structures through which plasma is filtered to form urine?


D
Urinary space
Bowman's capsule
Epithelial cell (podocyte)
Parietal epithelium
Capillary loops
Endothelial cell
Mesangial cell
Mesangial matrix
Angiotensin II vasoconstricts
Prostaglandins vasodilate
Efferent arteriole
Juxtaglomerular apparatus
Afferent arteriole
Macula densa
E

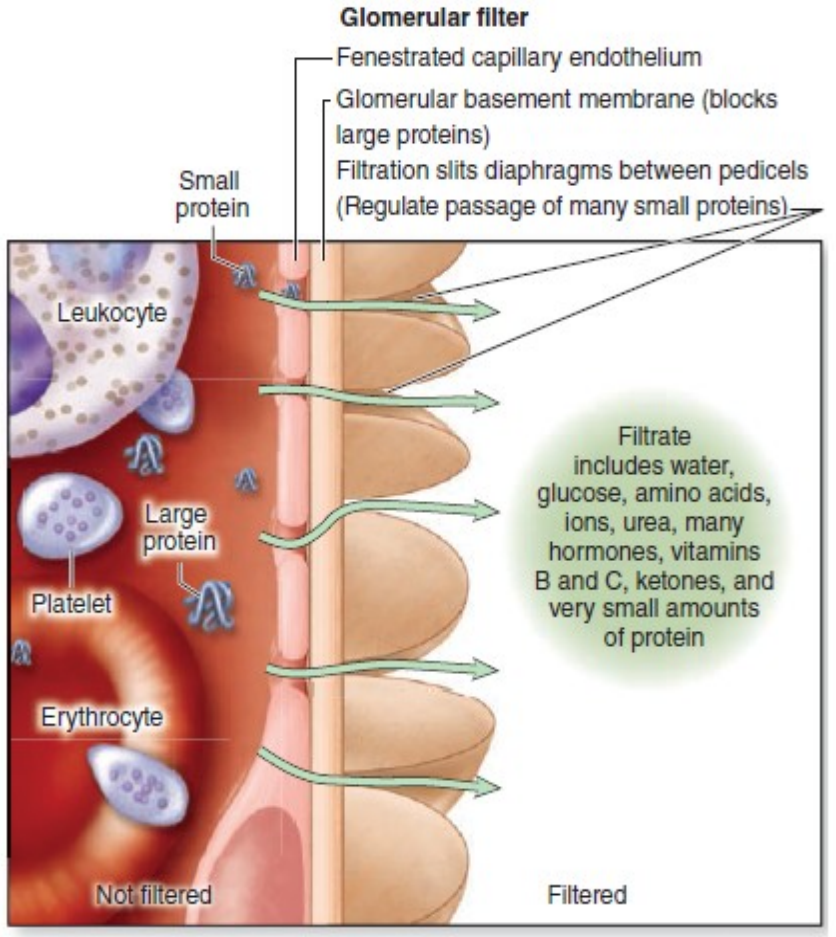
Glomerular Basement Membrane

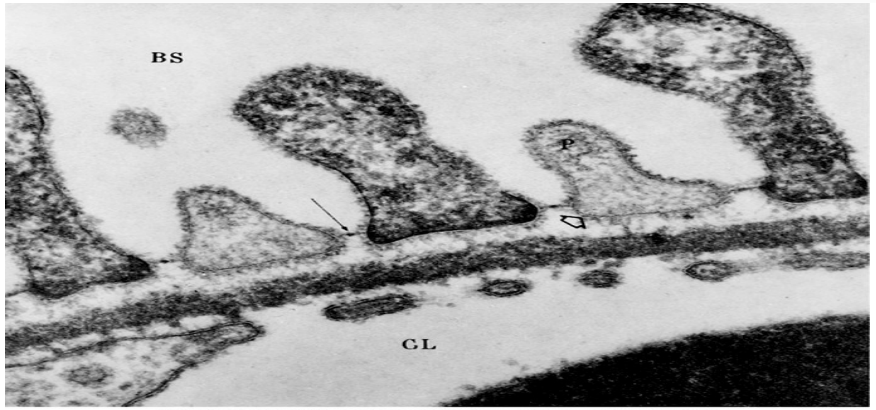
- **Central electron dense layer:-**
  - Lamina densa.
  - Formed of collagen IV
  - Acts as **physical** barrier “restrict passage of **large proteins**”
- **Outer & inner electron lucent layers:-**
  - **Lamina rara externa**: adjacent to podocyte
  - **Lamina rara interna**: adjacent to endothelial cells
  - It acts as **charge** barrier “restrict passage of **organic anions**”.



Blood Renal Barrier

- **Fenestrated endothelial cells:** act as sieve plate, stop passage of blood cells and platelets.
- **Glomerular basement membrane:** allow passage of small molecules & stop passage of large proteins.
- **Filtration slit diaphragm:** stop passage of many small proteins





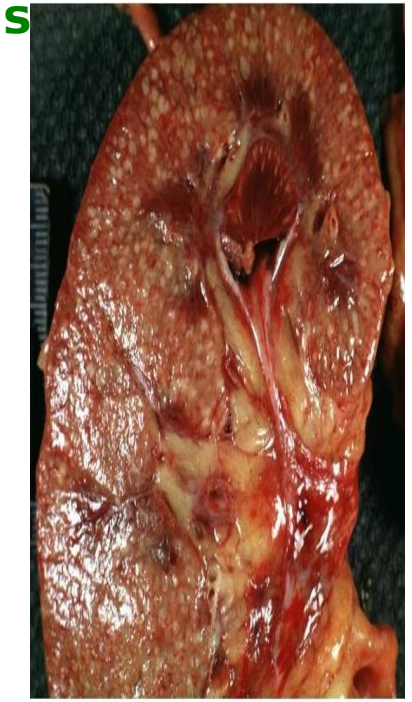
10- What is the pathogenesis of diabetic nephropathy & chronic kidney disease in Magdy?

Diabetic nephropathy

1. Pyelonephritis (PN) (acute or chronic) & papillary necrosis (special pattern of acute PN)

due to low immunity and increased susceptibility to infections & neurogenic bladder dysfunction

Pyelonephritis

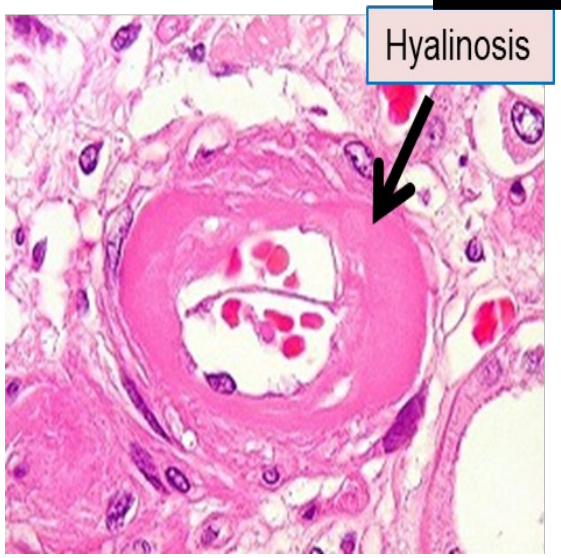


Papillary necrosis

2. Atherosclerosis of renal artery

due to

- Disturbance of fat metabolism
- Advanced glycation end products(AGEs) that accelerate atherosclerosis (help LDL to be trapped in the vessel wall)

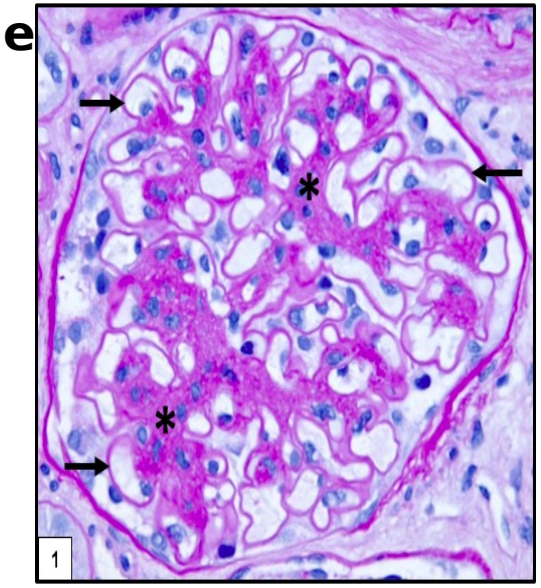


3. Hyaline arteriolosclerosis of afferent and efferent arterioles

Hyaline thickening of wall of arterioles with narrowing of lumen due to associated hypertension (leakage of

4. Glomerulosclerosis in long standing uncontrolled cases

Diffuse glome

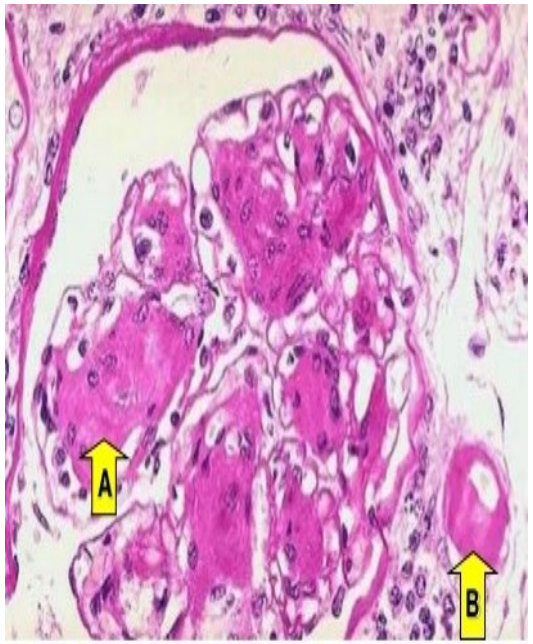


➢ Diffuse glomerulosclerosis

- Diffuse increase in mesangial matrix* **associated with**
- Diffuse thickening of glomerular capillary basement membrane **(microangiopathy)** → loss of protein in urine **(Nephrotic syndrome)**

(N.B): Microangiopathy :

- Diffuse thickening of glomerular capillary basement membrane by hyaline material composed predominantly of collagen type IV due to persistent hyperglycemia resulting in AGEs and TGF-B
- Despite thickening, the capillaries are more leaky than normal to plasma protein



A: Nodular glomerulosclerosis.
B: Hyaline Arteriolosclerosis.

➢ Nodular glomerulosclerosis (kimmelstiel Wilson lesion)

5
3

5. End stage kidney & chronic renal

Urine analysis:

24 hours collection of urine for protein

A/C ratio or 24 hours urine proteins

Albuminuria 2000mg/24hr (N < 30mg/24hr).

What is significance of microalbuminuria?

Urine Test: Microalbumin-to-Creatinine Ratio

Evaluating patients with Diabetes for kidney disease

$$\frac{\text{Urine albumin (mg/dL)}}{\text{Urine creatinine (mg/dL)}} \longrightarrow \text{X 1000}$$

mg microalbumin/g creatinine)

(normal less than 30 mg microalbumin/g creatinine)

HCO_3: 18mEq/L N: (23- 30 mEq/L)

What is the Mechanism of Kidney in regulation of Acid Base Balance?

Renal mechanisms in control of acid-base balance

- 3rd line of defense, most potent and most efficient mechanism.
- The kidneys play two major roles in the maintenance of normal acid-base balance:
- In normal metabolism and acidosis:
  - Increase reabsorption of HCO_3^-
  - Increase secretion of H^+:

  (1) Excretion of H^+ as titratable acid (i.e., buffered by urinary phosphate)

  (2) Excretion of H^+ as NH_4^+.

secretion of H^+ by either mechanism is accompanied by synthesis and reabsorption of *new* HCO_3^-

- In case of alkalosis decrease the reabsorption of HCO_3^- and decrease secretion of H^+

11- What do you expect the acid-base status in Magdy?

What is the state of Anion Gap in this case?

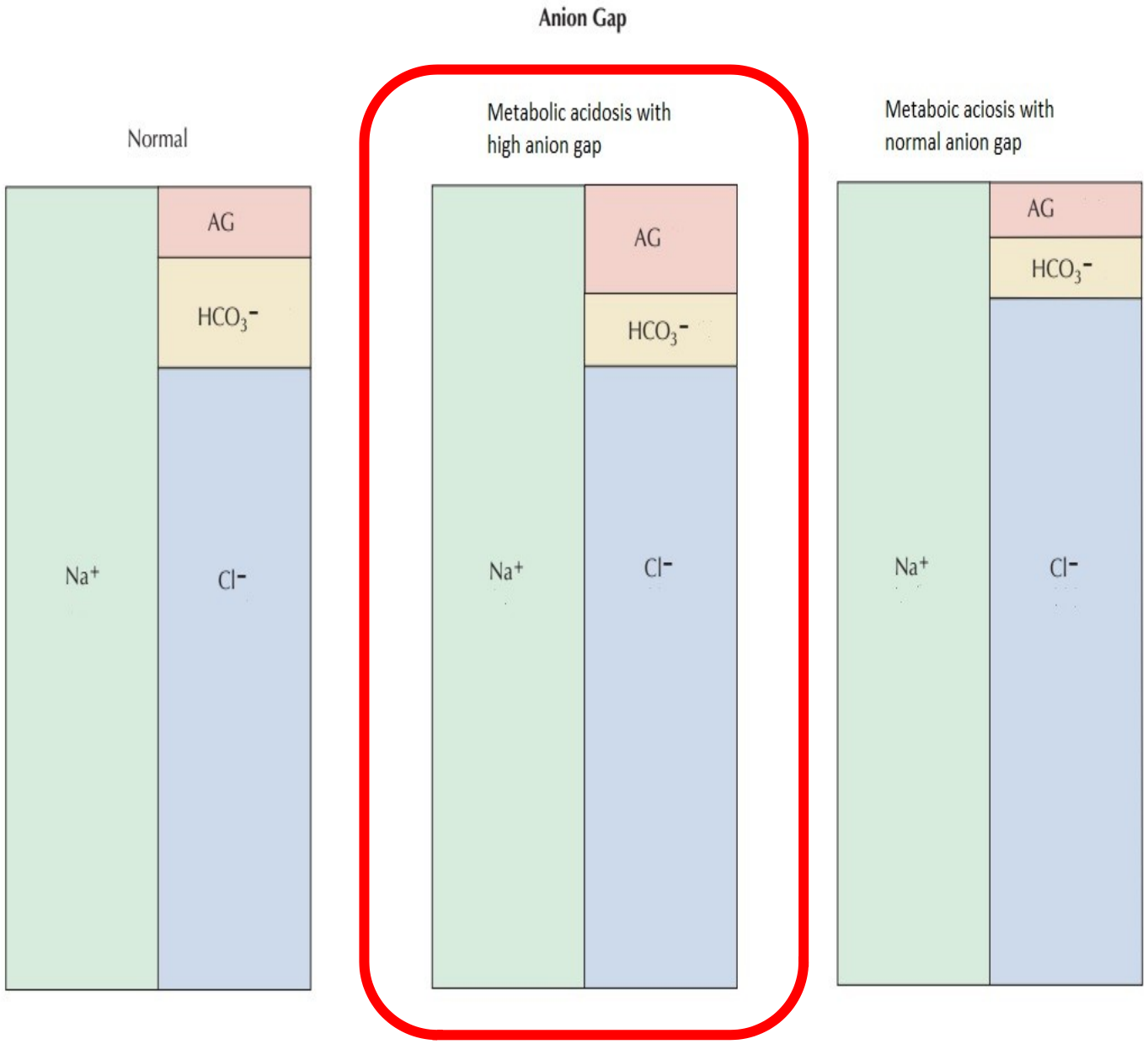
- The expected acid-base status in Magdy is ***Metabolic acidosis***

Patient has (***low HCO_3^-***)impaired kidney function

- **The state of Anion Gap in this case**

$$\text{Plasma anion gap} = [Na^+] - ([HCO_3^-] + [Cl^-])$$

The normal range of the plasma anion gap is ***8–16 mEq/L***


Anion Gap
Normal
Metabolic acidosis with high anion gap
Metaboic aciosis with normal anion gap
AG
HCO_3^-
Na^+
Cl^-
AG
HCO_3^-
Na^+
Cl^-
AG
HCO_3^-
Na^+
Cl^-

My legs are swollen

The doctor prescribed to Magdy:

- **Lisinopril**
- **Modified the insulin dose**

The doctor advised Magdy to:

- **Avoid intake of analgesics**
- **Diet** should be of **low salt** and **low protein** content.

He emphasized on Magdy to **follow up** after 3 months.

The doctor advised Magdy to:

- Avoid intake of analgesics
- Diet should be of **low salt** and **low protein** content.

He emphasized on Magdy to follow up after 3 months.

Comment

- He should avoid nephrotoxic drugs.
- Diet low in protien , low in salt for (oedema and hypertension).
- Low in saturated fat and trans fat (hydrogenated oils) as he is dyslipidemic.
- Fluid balance is very important :
- Urine output + 500ml.
- Treat anemia according to the type (mostly will be IDA).
- Treat hypocalcemia with calcium and active vitamin D.
- Frequent follow up till stabilization of the condition.

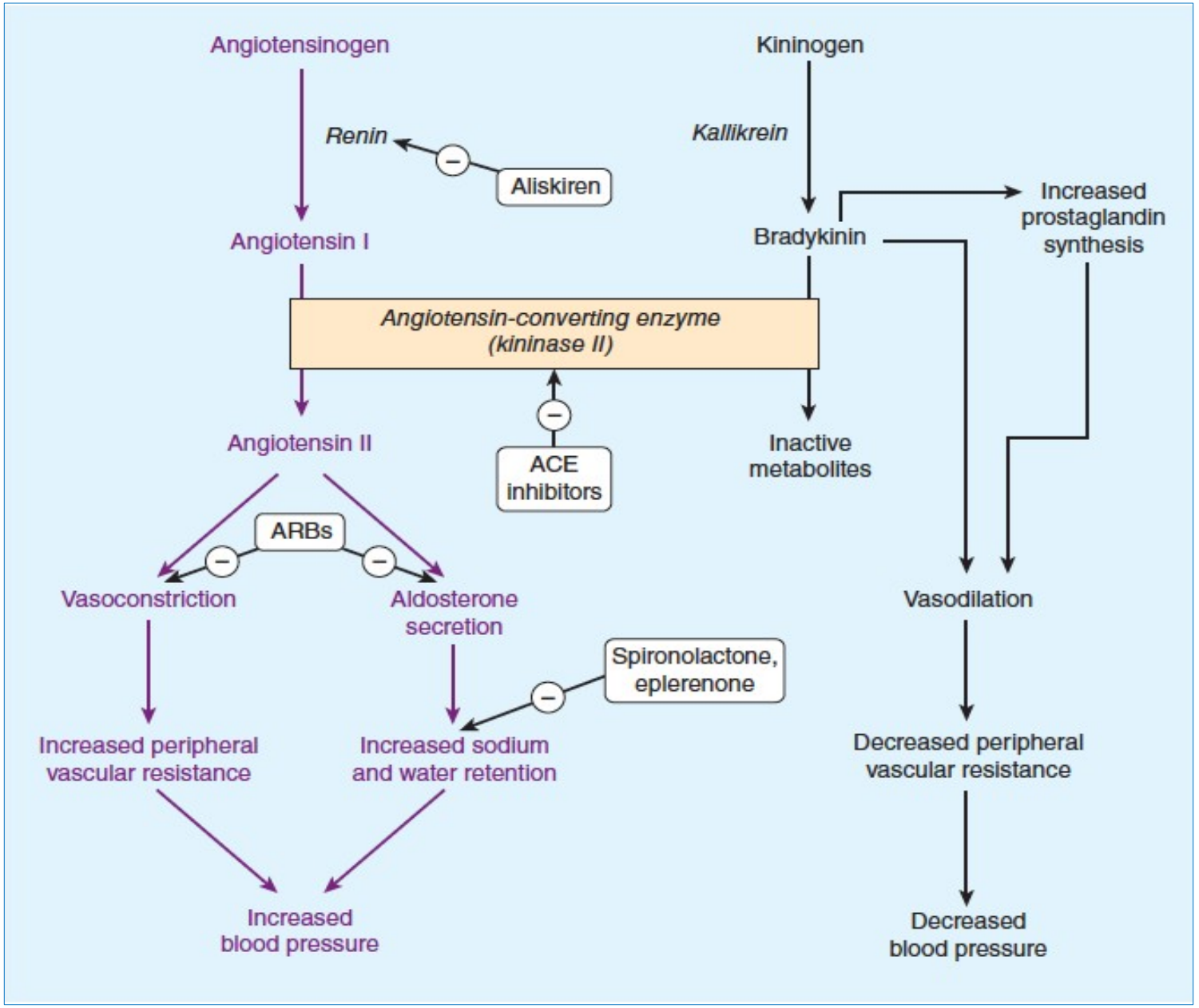
Why did the doctor prescribe Lisinopril?

Lisinopril

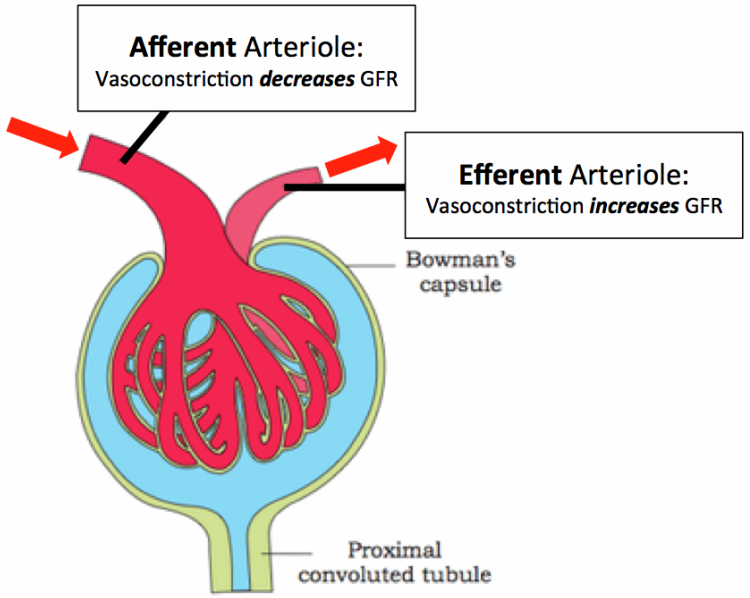
- The **ACE inhibitor** *Lisinopril is an* antihypertensive drug

- It is particularly valuable in diabetes because they diminish proteinuria and stabilize renal function

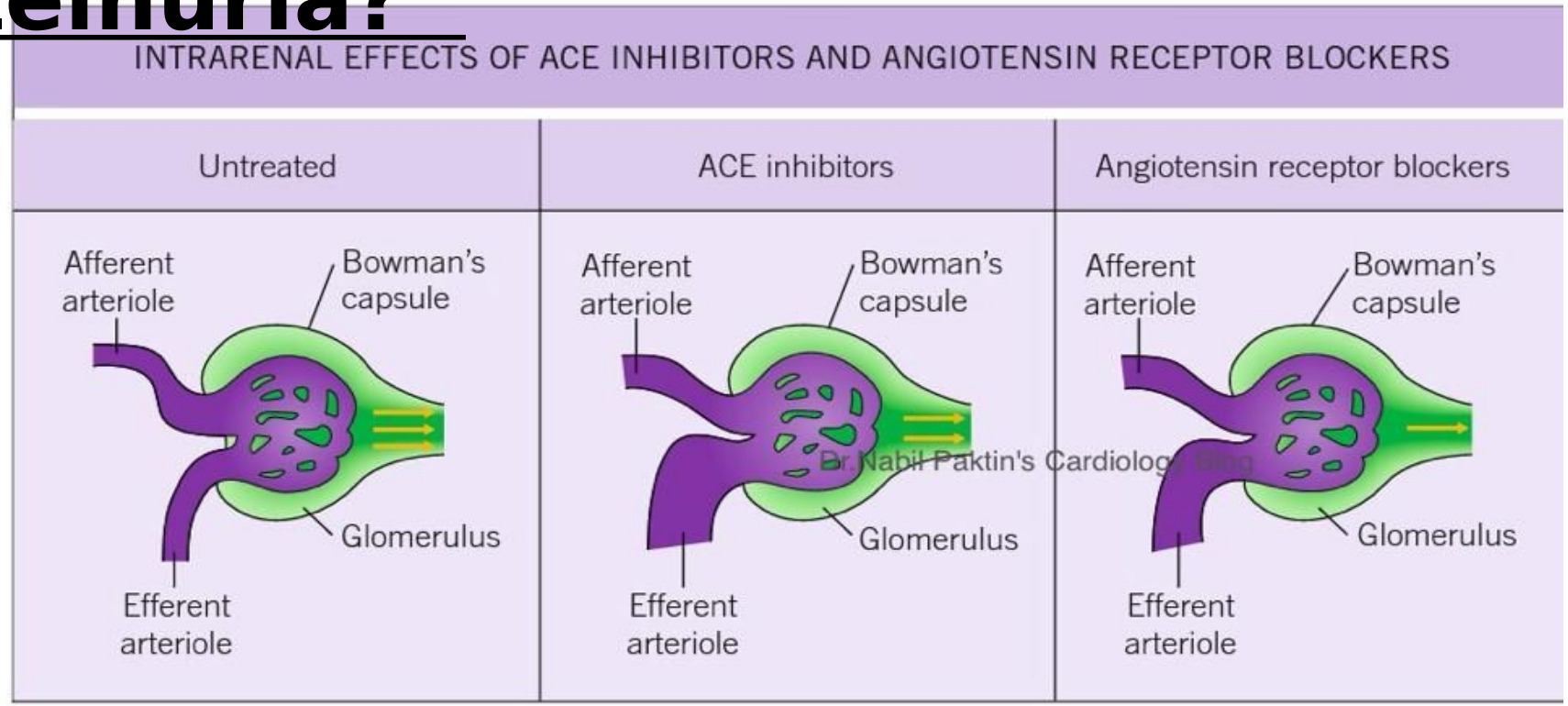
- Lisinopril has Longer t1/2 than Captopril so it can be used once or



How ACEIs reduce proteinuria?



Microvascular modulation of glomerular filtration rate (GFR)



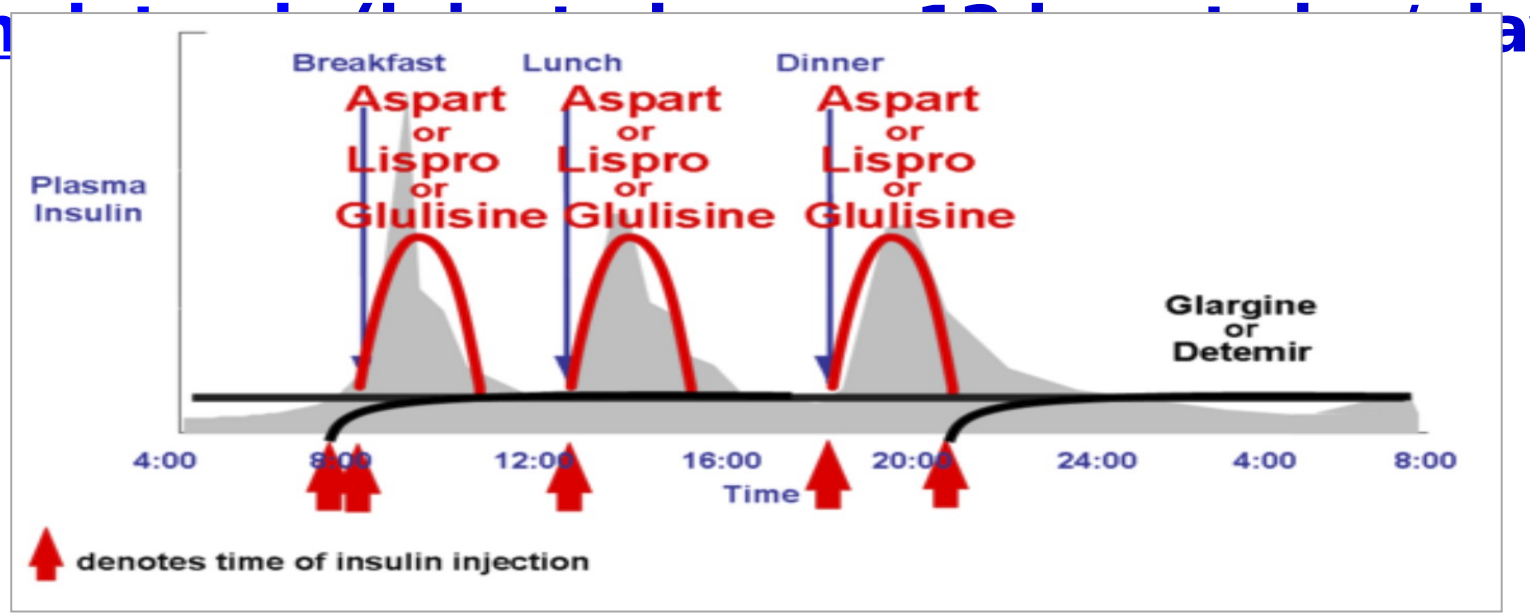
important precautions for ACE inhibitors:

- Hyperkalemia, more likely to occur in patients with renal insufficiency or diabetes K^+ must be measured regularly
- Dry cough sometimes accompanied by wheezing, and angioedema; (due to ↑↑Bradykinin) could occur NOT in Asthmatic patients
- Congenital bilateral renal artery stenosis must be excluded otherwise Acute renal failure

What is the insulin regimen that could be used in the uncontrolled blood glucose in diabetic patients?

Multiple daily injections: (basal – bolus regmin)

- The administration of **3/more insulin injections**/day.
- **Ultrashort Acting** insulin analogs (insulin-**lispro or aspart**)
  or **Short acting (Regular insulin)** must be given in **THREE** pre-meals injections
- **+ injection of Long-acting insulin analogs** such as:
  insulin glargine (injected once / day - at night)
  OR insulin



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IMPORTANT NOTE :

The doctor must be sure that the patient follow the Insulin Injection Instructions:

1- Insulin is protected from Heat & Freezing.
2- The patient Does Not Shake insulin
3- The site of SC injection

Take home message

- **Never to take analgesics**

- ***Low salt, low K and low protein diet in patients with kidney disease***

- ***Follow up of blood pressure and blood sugar level***

- ***Guidelines and evidence based medicine***


Thank
you